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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/706,778	11/07/2000	Daniel Bichon	1201-83	6925

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EXAMINER
SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/706,778	BICHON ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/7/2000, 11/29/2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-50* is/are pending in the application.

4a) Of the above claim(s) *3-31,37,38 and 45-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36 and 39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *3-31,37,38 and 45-50* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *07/695,343* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group III, claims 32-50 in Paper No. 7 is acknowledged.

Claims 3-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Applicant's election of the species of biodegradable polylactide/glycolide or polypeptide polymer membrane and the elected filler of air and freon is also ackinowledged. Accordingly, the search is directed to these species. Claims 37-38, 45-50 are further withdrawn from consideration because they are directed to the non-elected species. Claims 32-36 and 39-44 are now under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-35, 42-44 and all dependent claims thereof are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "a few nanometers" and "several thousands of nanometers" in claim 34 are relative terms which render the claim indefinite. Said terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the

scope of the invention. In the instant case, such terms include numerous possible measurements from two or three nanometer to thousands of centimeters. Thus, the metes and the bounds of the recitation is not clear.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 42 and 43 recpectively recite the broad recitation phospholipids and polyalkylene glycols, and the claim also recite "lecithins" and "polyethylene glycol" which is the narrower statement of the range/limitation.

Claim 41 recites the phrase "and the like" in line 2 of the claim. Such phrase renders the claim vague as it is not clear what is encompassed by such phrase. Accordingly, the metes and bounds of the claim is not clear.

Claim 44 contains the trademark/trade name "Freon". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a gas and, accordingly, the identification/description is indefinite.

Freon is a trademark for any of various nonflammable gaseous or liquid fluorocarbons by Dupont Chemicals. The scope of this trademark changes as newly formulations are assigned numbers within this class of chemicals, e.g. Freon-11, Freon-12, Freon –114. Thus, the metes and bounds of the claim is not clear.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32-36, 39-44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,333,021; claims 1-22 of US Patent 6,200,548; claims 1-24 of US Patent 6,136,293; claims 1-17 of US Patent 6,123,922; claims 1-50 of US Patent 6,110,443; claims 1-13 of US Patent 5,840,275; claims 1-16 of US Patent 5,658,551; claims 1-19 of US Patent 5,271,928. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scopes of each of the patented claims overlap with the instant pending claims; thus, rendering the instant pending claims an obvious variant of the patented claims.

The instant claims are directed to dry microballoons which upon dispersion in an aqueous carrier liquid form aqueous dispersions comprising microballoons having 50-500nm thick polymer membrane filled with air or gas, wherein the microballoons have a mean size in the range of a fraction of micron to 1000 microns and wherein the polymer membrane comprise a biodegradable synthetic polymer, additives selected from phospholipids, hydrophobic compounds, polyalkylene glycols and the like compounds.

The compositions of each of the patented claims overlap with the instant compositions to the extent that they are directed to microballoons for the same intended use, possessing similar characteristics and comprising the same polymeric membrane material, gaseous compounds, and additives.

For example, the claims of US Patent 6,333,021 ('021) are directed to substantially the same microcapsules having a mean size from a fraction of micrometer to 1000 micrometers, a 50-500 nm thick solid membrane wall encapsulating air or a gas wherein the polymeric moieties such as polylactide/polyglycolide copolymers or polypeptides may be included within the polymeric membrane-forming shell (see claims 1-14).

The pending claims differ from the patented claims as they do not explicitly use triglyceride moieties in their membrane-forming material. Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to prepare membrane-forming shell material comprising a synthetic polymer, because as suggested in the '021, the ordinary skill in the art would have had a reasonable expectation to succeed in improving the surface active properties of microballoons and thus, the stability of microballoons when incorporating a polymeric moiety into the membrane-forming shell material of the patented claims.

Similarly the claims of US Patent 5,271,928 ('928) are directed to compositions comprising substantially similar compositions comprising similar precursors as of those used in the instant claims. The difference between the pending claims and the patented claims is in the explicit microbubble size of the instant claims. However, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the size of the microbubbles taught in '928 to enhance the delivery of the compositions to the body cavities of interest, thus, improving their intended use.

Claims 32-36, 39-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of copending Application No. 09/225,293; claims 1-35 of copending Application No. 09/253,536; claims 1-7, 9, 14, 16, 18-19, 23 of copending Application No. 09/266,889; claims 1-8 of copending Application No. 09/401,835; claims 1-29 of copending Application No. 09/401,836; claims 1-5, 17-20 of copending Application No. 09/401,838. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scopes of claims for each of the copending application substantially overlap with the instant pending claims; thus, rendering the instant pending claims an obvious variant of each other.

For example the claims of the copending application no. 09/401,835 is directed to aqueous contrast agents comprising microbubbles comprising a polymeric surfactant, freon gas, an aqueous carrier. The difference between the claims of the copending applications and the instant application mostly relies on the size of the dispersed microballoons. However, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the size of the microballoons in order to improve the delivery amounts of microballoons when delivered in vivo.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32-36, 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feinstein US Patent 4,774,958 or Temple US Patent 4,089,800 in view of Ganguly et al (J. Microencapsulation, 1989, 6:2:193-198).

The instant claims dry microballoons comprising a synthetic biodegradable polymer that upon dispersion in an aqueous carrier liquid form an aqueous dispersion comprising microballoons having a mean size in the range of a fraction of micron to 1000 microns and having a porosity of 50-2000nm and being deformable and resilient.

Feinstein teaches protein microbubbles which have synthetically been altered by heat denaturation or chemical fixation (col 5, lines 9-32). The polymeric moiety of Feinstein meets the limitations of instant polypeptides. The diameters of Feinstein's microbubbles of Feinstein are in the range of 4-5 microns (col 5, lines 1-7). However, Feinstein fails to specifically teach the instant wall thickness and membrane porosity.

Temple teaches void containing microcapsules having a diameter of from about 0.1 to about 25 microns (see col 10, lines 15-25). Temple uses a conventional methods of spraying or atomizing the polymeric solution to prepare his dry microcapsules (see col 9, lines 40-67; col 10, lines 30-40). Temple also teaches the use of other additives including ethylene glycols to the polymeric membrane of his compositions (col 6, lines 13-60). Temple fails to specifically teach the instant wall thickness or porosity.

Ganguly also teaches conventional process of preparing hollow polystyrene microspheres (abstract) including the methods employed by Temple. The microspheres of Ganguly are prepared by modified interfacial polymer depositions methods (see page 194). Ganguly specifically teaches that the wall thickness and porosity of the microspheres are a function of polymeric concentration ant the presence of the solvent on the surface of the microsphere (see page 197, 2nd paragraph; page194 under subheading Results and discussion; figure 2). Accordingly, optimizing the porosity and wall thickness of microspheres are well within the purview of an ordinary artisan.

The teachings of Feinstein, Temple, and Ganguly are viewed to be in the same field of endevour, as they all teach various methods of preparing microbubbles for in vivo administeration.

Although, Feinstein and Temple fail to specifically teach the exact claimed wall thickness and porosity, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the wall thickness and surface porosity of the microsbubble of Feinstein or microcapsules of Temple, as suggested by Ganguly. One

of ordinary skill in the art would have been motivated to do such modifications to observe the optimal clinical effects of such microbubbles when administered in vivo.

Claims 32-36, 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feinstein US Patent 4,774,958 or Temple US Patent 4,089,800 in view of Ganguly et al (J. Microencapsulation, 1989, 6:2:193-198) as applied to claims 32-36 above, and further in view of Tickner US Patent 4,265,251.

The teachings of Feinstein, Temple and Ganguly are discussed above. Feinstein, Temple and Ganguly respectively fail to teach the use of Freon in their microbubbles, void containing microcapsules and microspheres.

Tickner teaches methods of ultrasound imaging using gas containing microbubbles (abstract, col 7, lines 11-54). Tickner teaches that although the preferred gas is carbon dioxide, however, other gases such as freons may be used in his contrast agents (col 6, lines 63-67). Tickner fails to specifically teach the use of polymers as the membrane-forming material. Tickner also does not teach the instant wall thickness and porosity measurements.

Although, Feinstein and Temple fail to specifically teach the exact claimed wall thickness and porosity, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the wall thickness and surface porosity of the microsbubble of Feinstein or microcapsules of Temple, as suggested by Ganguly, for the reasons described above. Furthermore, one of ordinary skill in the art would have been motivated to use other suitable gaseous compounds, such as Freon, as taught by Tickner, because the ordinary skill in the art would have had a reasonable expectation

to succeed in observing the similar clinical effects when using any suitable gas described in the art to provide the same results.

Claims 32-36, 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reinhardt et al US Patent 5,425,366 in view of Ganguly et al (J. Microencapsulation, 1989, 6:2:193-198) and Tickner US Patent 4,265,251.

The instant claims dry microballoons comprising a synthetic biodegradable polymer that upon dispersion in an aqueous carrier liquid form an aqueous dispersion comprising microballoons having a mean size in the range of a fraction of micron to 1000 microns and having a porosity of 50-2000nm and being deformable and resilient.

Reinhardt teaches methods of preparing gaseous microparticles for ultrasonic constrast imaging comprising denatured albumin or other suitable polymers such as polypeptides and polysaccharides (col 5, lines 20-55; example 25, col 13; col 16, lines 1-20). Reinhardt further teaches addition of other suitable additives into their polymeric moiety as a cryoprotector and then freeze drying his microparticles (see col 6, lines 19-50). Reinhardt teaches the thickness of his polymeric layer to be preferably in the range of 10-200 nm and a diameter size of up to 10 microns (col 4, lines 41-55). Reinhardt is a competent prior art as its teachings has an effective filing date, which is earlier than the effective filing date of the instant application (see [63]). Reinhardt also teaches the use of a liquid freon such as dibromodifluoromethane in his microparticles (see col 5, lines 62-63). However, Reinhardt fails to specifically teach the porosity of the instant polymeric units, and the use of gaseous freon.

Ganguly is used to solely show that modifying the wall thickness and porosity of hollow microspheres is conventional and well within purview of one ordinary skill in the art. Specifically, Ganguly teaches that the wall thickness and porosity of the microspheres are a function of polymeric concentration ant the presence of the solvent on the surface of the microsphere (see page 197, 2nd paragraph; page194 under subheading Results and discussion; figure 2). Accordingly, optimizing the porosity and wall thickness of microspheres are well within the purview of an ordinary artisan.

Tickner teaches methods of ultrasound imaging using gas containing microbubbles (abstract, col 7, lines 11-54). Tickner teaches that his preferred gas is carbon dioxide, but other gases such as freons may be used in his ultrasound contrast agents (col 6, lines 63-67). Tickner fails to specifically teach the use of polymers as the membrane-forming material. Tickner also does not teach the instant wall thickness and porosity measurements.

Although, Reinhardt fails to specifically teach the exact claimed porosity, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the wall thickness and surface porosity of the micro bubbles of Reinhadt by modifying the concentration of a polymer of choice, as suggested by Ganguly, because one of ordinary skill in the art would have been motivated optimize such characteristics of Reinhardt's microparticles to observe the optimal clinical effects of their *in vivo* utility.

Moreover, as freons are suitable substitute for air in gaseous microparticles used in the art of ultrasound contrast imaging, absence a showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to

replace the air used by Reinhardt with a gaseous freon, because as suggested by Tickner, the ordinary skill in the art would have had a reasonable expectation to succeed in formulating a stable contrast agent for ultrasound imaging.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie can be reached on 703-308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

Shahnam Sharareh, PharmD
Patent Examiner, Art Unit 1617

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